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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,778	YOSHINO ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,7-13,15,16 and 33-40* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,7-13,15,16 and 33-40* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on November 22, 2011.

Receipt of Declarations under 37 CFR 1.132 is acknowledged.

Status of Claims

Amendment of claim 1, 7-9, 13, cancellation of claims 3-6 and 14; and addition of claims 33-40 is acknowledged.

Claims 1, 7-13, 15-16 and 33-40 are currently pending and are the subject of this office action.

Claims 1, 7-13, 15-16 and 33-40 are presently under examination.

Priority

The present application is a 371 of PCT/JP05/001932 filed on 02/09/05, and claims priority to foreign application: JAPAN 2004-032420 filed on 02/09/2004 and JAPAN 2004-032421 filed on 02/09/2004.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment and/or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Prior Art: counterpart

WO 02/34264 is the PCT counterpart to US 6,933,310.

WO 02/34264 has a 102(b) date as a result of its May 2, 2002 publication date.

US 6,933,310 is prior art under U.S.C 102(e) as a result of its August 23, 2005 publication date.

Because WO 02/34264 and US 6,933,310 appear to have identical disclosures, and because the WO document was published in Japanese language designating the United States, the US Patent US US 6,933,310, which is the National Stage entry of WO 02/34264 is being used as a translation of WO 02/34264 PCT. As such, any reference hereinafter to column and line numbers will be based upon the US Patent, but should be interpreted as referring to the corresponding disclosure of the aforementioned PCT counterpart.

Claim Rejections - 35 USC § 103 (New Rejection Necessitated by Amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 7-12, and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshino et. al. (Neurological Therapeutics (2003) 20:557-564, cited by Applicant, translated from Japanese, cited in prior office action).

For claims 1 and 7, Yoshino teaches a method of treating Amyotrophic Lateral Sclerosis (ALS) comprising the administration of ederavone (3-methyl-1-phenyl-2-pyrazoline-5-one) (see title for example). Yoshino further teaches the following dose regimen: 14 day administration and then 10 days each month on a long term basis (see page 5, first two lines and page 10, lines 5-9). Finally, Yoshino further teaches the following dose regimen: 20 day administration Monday through Friday (see page 12, lines 6-9), which translates in 5 day administration (Monday through Friday) and 2 day holiday period (Saturday and Sunday).

In summary, Yoshino teaches a regular dose regimen consisting of 10 day administration followed by 20-21 days of holiday period, and also teaches a dose regimen consisting of 5 day administration followed by 2 days of holiday period.

These dose regimens are very close to the dose regimen of the instant claims. MPEP 2144.05 states: "A *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of*

America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)." Further, in the instant case it's within the capability of the ordinary artisan to determine the optimal dose regimen for a particular patient and adjust the dose regimen based on the observed clinical effectiveness, thus resulting in the practice of claims 1 and 7 with a reasonable expectation of success.

For claims 8 and 33, Yoshino further teaches the administration of 30/mg per day of ederavone (see page 12, last paragraph) which anticipates the dose range of claims 8 and 33.

For claims 9 and 34, Yoshino further teaches the administration of 30/mg per day of ederavone (see page 12, last paragraph) which is close to the 60 mg dose in claims 9 and 34.

.MPEP 2144.05 states: "A *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing

alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)." Thus resulting in the practice of claims 9 and 34 with a reasonable expectation of success.

For claims 10 and 35, Yoshino further teaches that ederavone was administered once daily (see page 5, first two lines).

For claims 11-12 and 36-37, Yoshino further teaches the administration of ederavone by continuous intravenous drip (see page 5, first two lines).

2) Claims 15-16 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshino et. al. (Neurological Therapeutics (2003) 20:557-564, cited by Applicant, translated from Japanese, cited in prior office action) as applied to claims 1, 7-12, and 33-37 above further as evidenced by Ikeda (WO 02/34264, cited by Applicant, which is the PCT counterpart to US 6,933,310, see above prior art counterpart, cited in prior office action).

Claims 15-16 further limit claim 1 and claims 39-40 further limit claim 7, wherein certain symptoms caused by ALS like: decreased respiratory function, voice and speech disorders, dysphagia, or upper and lower extremity motor disorders are being treated. However, the above symptoms are a characteristic of ALS as evidenced by Ikeda and do not further limit the claims. Ikeda teaches that that ALS often begins at middle age,

and is a lethal intractable disease, in which the condition rapidly deteriorates from muscular atrophy and muscle weakness to, finally, death due to respiratory insufficiency or the like in a matter of a few years (see column 1, lines 28-34). Ikeda further teaches that ALS is a cryptogenic disease mainly characterized by muscular atrophy and fasciculation. The initial symptoms mainly include hand weakness, dyskinesia in the digits and hands, and fasciculation in the upper limbs, And ALS can be classified into upper limb type, bulbar type, lower limb type and mixed type according to onset site. With any type of the disease, muscle groups of the whole body are impinged with the progress of the symptoms (see column 4, lines 27-38).

3) Claims 13 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshino et. al. (Neurological Therapeutics (2003) 20:557-564, cited by Applicant, translated from Japanese)) as applied to claims 1, 7-12, and 33-37 above further in view of Ikeda (WO 02/34264, cited by Applicant, which is the PCT counterpart to US 6,933,310, see above prior art counterpart, cited in prior office action).

Yoshino teaches all the limitations of claims 13 and 38, except for the specific rate of administration of ederavone. However, Ikeda teaches a method of treating ALS comprising the administration of ederavone (see for example claims 1-5). Ikeda further teaches that: the dose of the medicament can be selected according to various conditions including type of disease being treated, progress of the disease or degree of the symptoms, and age and weight of the patient. In general approximately 0.01 microgram/kg to 10 mg/kg per day for an adult is administered by injection or drip (see

column 5, lines 52-63). These dose regimens are very close and/or overlap with the dose regimens of claims 13 and 38.

MPEP 2144.05 states: In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990. MPEP 2144.05 further states: "A *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)." Thus resulting in the practice of claims 13 and 38 with a reasonable expectation of success.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

The declaration under 37 CFR 1.132 filed on November 22, 2011 is insufficient to overcome the rejection of claims 1, 7-13, 15-16 and 33-40 based upon 35 U.S.C. 103 (a) as set forth in the last Office action.

For a full response to the arguments presented by Takatomo Yoneoka, please see discussion below.

Applicant argues that:

As discussed on page 2 of the Declaration submitted herewith, Yoshino et al. does not teach or suggest a dose regimen in accordance with Applicants' claims. In fact, when the drug administration of Yoshino et al. is 14 days, the drug holiday period is unknown. Further, as discussed on pages 3 and 4 of the Declaration submitted herewith, a dosing regimen in accordance with Example 1 of the present specification (14 day drug period, followed by 14 day holiday period, followed by 10 day drug period, excluding Saturdays, Sundays and holidays) has unexpectedly superior results when compared to the dosing regimen disclosed in the Open Administration Trials of Yoshino et al. Specifically, edaravone suppressed the decline of the ALSFRS-R score for 6 months by 1.7 points in the Open Administration Trials of Yoshino et. al., while edaravone suppressed the decline of ALSFRS-R score for 6 months by 2.3 points in Example 1 of Applicants' specification. Thus, Example 1 of Applicants' specification is unexpectedly superior by 0.6 points.

As also discussed on page 4 of the Declaration, it is reported that 1 point of ALSFRS-R score increases the risk of death or tracheotomy by 7%. Thus, it is clear that the 0.6 point difference noted above is very significant for ALS patients.

MPEP 2144.05 teaches, "Applicants can rebut a prima facie case of obviousness based on overlapping ranges by showing the criticality of the claimed range. 'The law is

replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims .... In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.' In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)."

In this case, the Yoshino et al. reference fails to teach a dosing regimen in accordance with Applicants' amended claims. However, the Examiner has taken the position that Applicants' claims are obvious, because the claimed ranges and the prior art ranges do not overlap, but are close enough that one skilled in the art would have expected them to have the same properties. (Please see the last paragraph on page 11 of the outstanding Office Action.). However, as discussed above, the dosing regimen recited in Applicants' claims provides unexpectedly superior results when compared to the dosing regimen of the Yoshino et al. reference. Accordingly, contrary to the position of the Examiner, the ranges set forth in Applicants' claims do not have the same properties as the ranges set forth in the cited reference. Thus, Applicants have demonstrated the criticality of the recited ranges, and have thus rebutted any showing of obviousness set forth by the Examiner. Accordingly, it is clear that the invention of claims 7 and 9 is patentable over Yoshino et al.

Examiner's response:

MPEP 716.02 states:

"Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties

differ to such an extent that the difference is really unexpected. In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) (differences in sedative and anticholinergic effects between prior art and claimed antidepressants were not unexpected). In In re Waymouth, 499 F.2d 1273, 1276, 182 USPQ 290, 293 (CCPA 1974), the court held that unexpected results for a claimed range as compared with the range disclosed in the prior art had been shown by a demonstration of "a marked improvement, over the results achieved under other ratios, as to be classified as a difference in kind, rather than one of degree."

MPEP 716.02(c) states:

"Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978.).

Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) (Claims were directed to a display/memory device which was prima facie obvious over the prior art. The court found that a higher memory margin and lower operating voltage would have been expected properties of the claimed device, and that a higher memory margin appears to be the most significant improvement for a memory device. Although applicant presented evidence of unexpected properties with regard to lower peak discharge current and higher luminous efficiency, these properties were not shown to have a significance

equal to or greater than that of the expected higher memory margin and lower operating voltage. The court held the evidence of nonobviousness was not sufficient to rebut the evidence of obviousness.); In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (Evidence of improved feed efficiency in steers was not sufficient to rebut prima facie case of obviousness based on prior art which specifically taught the use of compound X537A to enhance weight gain in animals because the evidence did not show that a significant aspect of the claimed invention would have been unexpected.)".

MPEP 716.01(d) states:

"Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988), cert. denied, 493 U.S. 814 (1989); Richardson-Vicks, Inc., v. The Upjohn Co., 122 F.3d 1476, 1484, 44 USPQ2d 1181, 1187 (Fed. Cir. 1997) (showing of unexpected results and commercial success of claimed ibuprofen and pseudoephedrine combination in single tablet form, while supported by substantial evidence, held not to overcome strong prima facie case of obviousness). See In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984) for a detailed discussion of the proper roles of the examiner's prima facie case and applicant's rebuttal evidence in the final determination of obviousness".

In the instant case, the evidence presented by Applicant (see for example Table 1 above) is not sufficient to overcome the obviousness rejection for the following reason:

The data presented by Applicant in the 132 declaration: an ALSFRS-R score superior by 0.6 points under the instant dose regimen when compared to the dose regimen of the prior art (Yoshino et. al.) which translates in a decrease of death by tracheotomy by about 4%, cannot be considered significant enough or "unexpected" when considering such a strong case of obviousness: Yoshino teaches all the limitations of the instant claims (disease being treated and rug used) except for the dose regimen. Even the dose regimen of the prior art and the instant claims seem to be very similar, and as such it is expected some differences in some properties like the ALSFRS-R score. As stated in MPEP 716.01(d): "Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. In this case the evidence presented by Applicant is not sufficient enough to overcome the strong case of obviousness based on Yoshino et. al.

Withdrawn Rejections and/or Objections

Claims rejected under 35 USC 112, first paragraph (written description).

Due to applicant's amendment of the claims, the written description rejection is now moot.

Rejection under 35 USC 112, first paragraph (written description) is withdrawn.

Claims rejected under 35 USC 112, second paragraph.

Due to applicant's amendment of the claims and cancellation of claim 14, the 35 USC 112, second paragraph rejection is now moot.

Rejection under 35 USC 112, second paragraph is withdrawn.

Claims rejected under 35 USC 102 (b)

Due to Applicant's amendment of the claims, the Yoshino reference no longer anticipates the claims since Jiang does not teach the oral administration of Budesonide.

Rejection under 35 USC 102(b) is withdrawn.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS L SZNAIDMAN/
Primary Examiner, Art Unit 1628
December 12, 2011.